The Pharmacology of Sexual Function and Dysfunction
J. Bancroft, editor

Effects of alpha 2 antagonists on male erectile response.

J.Bancroft
MRC Reproductive Biology Unit, 37 Chalmers Street, Edinburgh EH2 9EW, United Kingdom.

Introduction

In the last ten years there has been increased interest within the pharamaceutical industry in the search for a pharmacological agent which enhances human sexual response. The main effort has focussed on the male. Attempts to explore dopaminergic agents have floundered because of significant problems with side effects. More recent attempts to explore serotonergic agents are at an early stage, and probably inhibited by the obvious complexity of the role of 5HT within the CNS. The class of drug which is receiving the most attention is the alpha-2 adrenoceptor antagonist, which in general has the advantage of being relatively free of non-specific side effects. For some time yohimbine, an alpha-2 antagonist, has been recognised as a potential enhancer of sexual response in men. A number of placebo-controlled studies of the drug in male sexual dysfunction have found some evidence of a sexually enhancing effect, albeit modest [1-5]. Each of these studies, however, has been notably lacking in any appropriate conceptual model for evaluating the direct effects of such a drug. Heterogenous groups of men with erectile dysfunction have been involved with no clear idea of what direct effect such a drug would be expected to produce or how to evaluate such an effect. This lack of a conceptual model for pharmacological effects on sexual response in the human contrasts with the situation on the rodent, where sophisticated analyses of drug effects, not only on particular categories of behavioural response, but also located in specific areas of the brain, are now possible [6].

As reported by Carani at this meeting, there is now consistent evidence of a distinction between androgen dependent and androgen independent erectile response systems in the human male, with spontaneous erections, such as nocturnal penile tumescence (NPT) manifesting the androgen dependent system, and erectile response to visual erotic stimuli (VES) the androgen independent system [7-11]. Given that alpha-2 adrenoceptor antagonists have been shown substantially to restore sexual behaviour after castration in the male rat, and that this effect can be demonstrated some months after castration [12], it has been suggested that the sexually arousing effect of androgens may be mediated by noradrenaline, perhaps particularly by modulation of alpha-2 tone. Thus when we were invited to evaluate experimentally the effects of a new alpha-2 antagonist on sexual response in men, the distinction between androgen dependent and androgen independent responses presented us

with a conceptual model on which to base our studies, leading to the hypothesis that this drug will enhance androgen dependent responses such as NPT and have little or no effect on androgen independent responses such as responses to VES. We set out to test this hypothesis by using two experimental paradigms; the effect of intravenous infusion of the drug, in two dosages, and compared with placebo, first on the erectile response to VES, and secondly, when infused through the night, on NPT.

In retrospect, our conceptual model was naively oversimplified. We had overlooked a paradox; whereas the rodent evidence had suggested that NA, and in particular alpha-2 antagonist action, could enhance central sexual arousal, we already knew that peripherally, noradrenergic tone inhibited sexual response, or at least erectile response, by maintaining tonic contraction of the sinusoidal smooth muscle [13]. We were perhaps less aware that NA mediation might also be involved centrally in maintaining this peripheral inhibitory tone. In other words, NA could be involved in both excitation and inhibition of sexual response. If that is the case, what should one expect when administering an alpha-2 antagonist systemically, with no ability to control where in the body or CNS it acts?

Let us consider the main findings, In each paradigm (i.e. response to VES and NPT) we investigated 12 normal volunteers and 24 men with probable psychogenic erectile dysfunction. The drug is a new alpha-2 antagonist, RS 15385, a potent specific alpha-2 antagonist with known central effects [14-16]. In both experiments we aimed for two plasma concentrations of the drug, 50ng/ml and 150ng/ml, which I will refer to as 'low' and 'high' doses.

Effect of the alpha-2 antagonist on erectile response to visual erotic stimuli.

Having first achieved and then maintained the target plasma concentration of drug (or placebo) with the infusion, we measured erectile, subjective and haemodynamic responses to a series of erotic stimuli, both fantasy and erotic film.

In our normal volunteers we found four significant effects of the drug: a) increase in spontaneous erections and b) increased subjective rating of sexual arousal, both *before* the presentation of erotic stimuli, c) prolonged tumescence in response to the visual erotic stimuli (see Fig 1) and d) increased systolic BP and heart rate both before and during erotic stimulation [17].

In our men with erectile dysfunction we found comparable but more modest effects of the drug, and when we divided our subjects into two age groups, around the median split of 45 years, we found no effect on either erection or haemodynamic response in the older men, and a modest significant effect in the younger men (Fig 2). When we examined the haemodynamic responses, we found that in our younger dysfunctional men during placebo

administration, blood pressure and heart rate responses to the erotic stimuli were blunted compared to the normal volunteers and the older dysfunctional men, and this blunting was largely eliminated by the high dose of the drug. This raises the possibility that a) there was a loss of responsiveness to the drug in the older dysfunctional men and b) there was a generalised increase of central alpha-2 tone in the younger dysfunctional men, which affected both erectile and haemodynamic response and was partially normalised by the drug [18]. (see Fig 3)

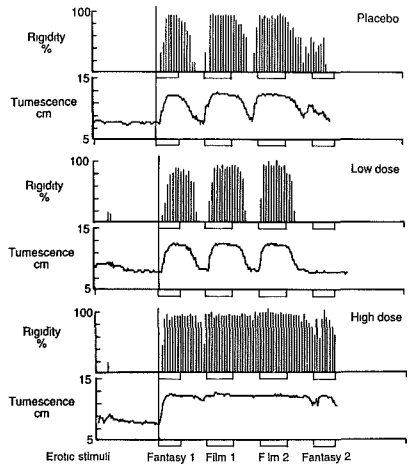
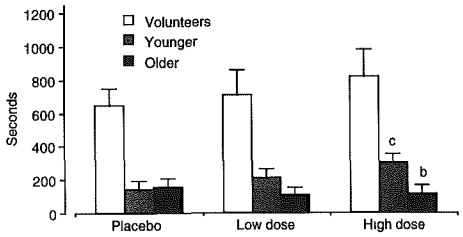


Fig 1. Erectile responses to erotic stimuli in one subject for the three conditions (Placebo, Low Dose and High Dose), showing penile circumference and rigidity changes for each session. This subject shows prolonged erection and failure to return to baseline during the neutral stimuli, with the high dose. (from Munoz et al [17])

Fig 2. Effect of drug on duration of erectile response. The time above 3cm increase in circumference for the younger and older dysfunctional men compared with the controls. b, younger > older, p<0.05; c, High > Placebo, p <0.01. (From Munoz et al [18])



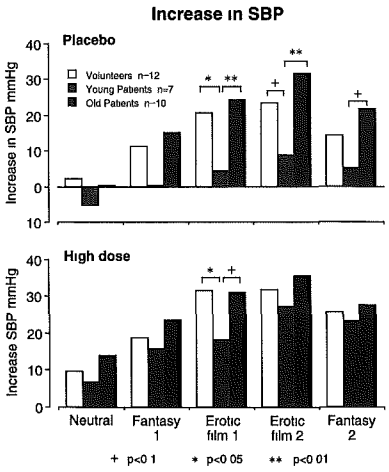


Fig 3. Comparison of systolic BP response in dysfunctional men and functional volunteers for placebo and high dose. + p<0.1, * p<0.05, ** p<0.01. (from Munoz et al [18])

Effect of the alpha-2 antagonist on Nocturnal Penile Tumescence.

The occurrence of erections during sleep is a well recognised phenomenon which has been widely used as a diagnostic test: normal NPT being taken as evidence of psychogenesis in erectile dysfunction. But there is a striking fact about NPT which, whilst well known has received surprisingly little attention. NPT occurs almost entirely during REM sleep. Why should that be the case?

Our knowledge of the physiological concomitants of REM sleep in humans is still sketchy, and there are likely to be species differences. However, animal data indicates the following consistently [19]:

REM sleep is associated with

1) 'Switching off' of NA neurones in the locus caeruleus, the central relay station of an extensive network in the CNS.

2) This is associated with a reduction in peripheral sympathetic activity, but only in certain parts of the body. These include the splanchnic vessels however, which would also include the vasculature of the penis.

3) Bursts of increased peripheral sympathetic activity occur in other parts of the body, presenting a picture of a dysregulated autonomic NS.

The 'switching off' of the locus caeruleus thus provides us with a possible explanation for the NPT, or at least its occurrence during REM sleep, because this could be associated with switching off the normal inhibitory tone of the penis. If this depends on the switching off of NA neurones, we should also pause to wonder what effect an alpha-2 antagonist might have on NPT. Will it increase NPT because of its central arousal effect, or will it inhibit NPT because it interferes with the NA 'switch off' during REM? What in fact did we find? [20]

In our young normal volunteers we found that a low dose of the drug enhanced NPT, though mainly during non-REM sleep, whereas the high dose of the drug reduced NPT, though mainly during REM (Fig 4). A curvilinear dose-response effect like this suggests a discrimination, by dose, between different receptors or systems, and we may well have been predominantly enhancing central arousal with the lower dose, and predominantly interfering with the REM 'switch off' with the high dose. In fact, the only positive effect of the high dose occurred in the interval between lights out and sleep onset, when there was an increase in erectile response - i.e. spontaneous erections in the waking state.

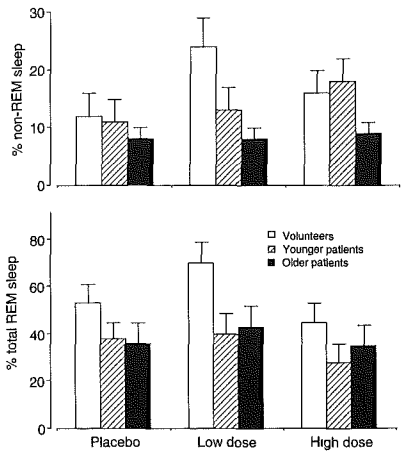


Fig 4. Comparison of normal volunteers and younger and older dysfunctional men in erectile response during non-REM and REM sleep, expressed as percentage of total time above 15mm increase in circumference. During non-REM sleep, we see a curvilinear dose effect in the volunteers, with a significant increase with low dose (Placebo v Low, $P<0.05$). In the younger patients we see a linear dose response effect, approaching significance with the high dose ($p=0.06$). There is no effect in the older patients. During REM, we find no effect in either group of dysfunctional men, and a trend ($p=0.09$) for the low dose in the volunteers. (From Bancroft et al. [20]

Next we gave the drug, using exactly the same protocol, to 24 men with psychogenic erectile dysfunction. This was a generally older group and once again we divided them into two age groups, younger and older, around a median split of 47 years. Again we found no effect of the drug in the older men, suggesting a possible age-related loss of responsiveness which might be aetiologically relevant. We did find a modest effect in the younger dysfunctional men, but subtly different to the volunteers. The dose-response effect was linear, the high dose enhanced NPT only during non-REM, and we observed no negative effect (Fig 4). Also the most noticeable time for the enhanced erectile response was between sleep onset and first REM, interestingly just after the onset of sleep, whereas in the volunteers, the positive effect of the high dose was just before sleep onset.

To explain this difference between our younger dysfunctional men and our controls we postulated a difference in the basal level of alpha-2 inhibitory tone in the two groups of men, effectively shifting the dose-response curve in the dysfunctional group (Fig.5) [21] Thus, in the dysfunctional men this increased tone would serve to inhibit the central arousal system, hence contributing to the erectile problem. The effect of the drug was to partially reduce this inhibitory tone and improve, though only modestly, the erections occurring during sleep.

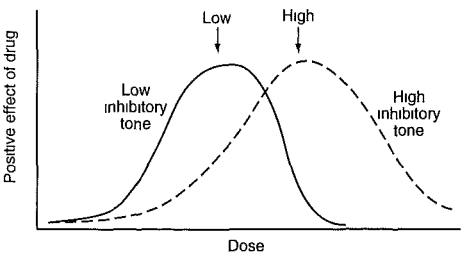


Fig 5. Hypothetical scheme to explain the different responses of the controls and the dysfunctional men. The controls, represented by the continuous line, had low alpha-2 inhibitory tone, and with the doses of drug used, showed optimum effect with the low dose. The dysfunctional men (broken line) had higher basal tone and showed a shift of the dose-response curve to the right. (from Bancroft [21])

Conclusions

These intriguing but complex findings should be regarded as preliminary. However, in both our experimental paradigms (i.e. response to VES and NPT) we found evidence suggestive of increased central inhibition in our younger dysfunctional men which, because of its response to the drug could well involve alpha-2 tone. Such inhibition may underlie the erectile problem in some younger men. The lack of response to the drug in the older men raises the possibility that an age related loss of responsiveness to the central arousing effects of NA may contribute to the general age related decline in erectile responsiveness, and may combine with other factors to lead to the assumed cases of 'psychogenic' erectile dysfunction in the older age groups.

These findings also remind us that we cannot assume a neurotransmitter is going to be confined in its effects to one system, and that different systems may actually be working against each other. In such circumstances, unless we target one specific system, which is usually not possible in human subjects, we cannot be sure what balance of effects will be produced by systemic administration of a drug. If, however, the curvilinear dose-response of this alpha-2 antagonist suggested in this study can be confirmed, and also demonstrated in the waking state as well as during sleep, then some degree of selectivity of system effect might be obtained by varying the dosage. And if indeed the positive effects are obtained with a lower and negative effects with a higher dosage we have a built in restraint of abuse of such drugs.

References

1. Reid K, Surridge DHC, Morales A, et al. Lancet, 1987; ii: 421-423.
2. Morales A,Condra M, Owen J A, Surridge D H, Fenemore J, Harris C. J Urol, 1987 137: 1168-1172.3.
3. Riley A J, Goodman R E, Kellet J MR, Orr R. Sexual and Marital Therapy, 1989; 4: 17-26.
4. Sonda L P, Mazo R, Chancellor M B. J Sex Marital Ther, 1990; 16: 15-21.
5. Susset J G, Tessier C D, Wincze J, Bansal S, Malhotra C, Schwacha M G. J Urol, 1989; 141: 1360-1363.
6. Everitt B J, Bancroft J. Annual Review of Sex Research, 1991; 2: 77-118.
7. Bancroft, J. and F. C. W. Wu. Arch Sex Behav, 1983; 12(1): 59-66.
8. Kwan M, Greenleaf W J, Mann J, Crapo L, Davidson J M. J Clin Endocrinol Metab, 1983; 57: 557-562.
9. O'Carroll R E, Shapiro C, Bancroft J. Clin Endocrinol, 1985 23: 527-538.
10. Carani C, Bancroft J, Granata A del Rio G, Marrama P. Psychoneuroendocrinology, 1992; 17: 647-654.
11. Carani C, Bancroft J, Granata A, Marrama P. 1994. Submitted for publication.
12. Clark, J T, Smith E R, Davidson J M. Physiol Behav, 1985; 35: 517-521.
13. Bancroft J. Human Sexuality and its Problems. 2nd Edition. Edinburgh: Churchill Livingstone, 1989.
14. Clarke RD, Repke DB, Berger J, Nelson JT, Kilpatrick AT, Brown CM, MacKinnon AC, Clague RU, Spedding M. J Med Chem, 1991; 34: 705-717
15. Brown C M, MacKinnon A C, Redfern W S, Hicks P E, Kilpatrick A T, Small C, Ramcharan M, Clague R U, Clark R D et al. Br J Pharmacol, 1993; 108: 516-525.
16. Redfern WR et al. Brit J Pharmacol, 1993; 108:437-442
17. Munoz M, Bancroft J, Turner M. Psychopharmacology, 1994; 115: 463-470
18. Munoz M, Bancroft J, Beard M. Psychopharmacology, 1994; 115: 471-477
19. Parmeggiania P L, Morrison A R. In: A.D Loewy and K.M. Spyer. eds Central Regulation of Autonomic Function, New York: Oxford University Press, 1990.
20. Bancroft J, Munoz M, Beard M, Shapiro C M. Psychosom Med 1994, (in press)
21. Bancroft J. Neurosc Biobehav Rev. 1994, (in press)

Discussion - EFFECTS OF ALPHA 2 ANTAGONISTS ON MALE ERECTILE RESPONSE

J. Stewart

One of the questions that I have has to do with the degree to which you think the alpha-2-antagonist is having its effects only at the auto-receptor. Your analysis is that its effects are to inhibit the normal inhibition on that system, but as you get into higher doses you may very well have postsynaptic effects.

J. Bancroft

That may be one mechanism whereby you shift from one type of effect to another, I have absolutely no idea of what the likelihood is there. Maybe someone else could comment on that. My understanding is that when you get a curvilinear dose response relationship it is sometimes due to a shift from predominantly presynaptic to postsynaptic effects.

B.J. Everitt

That might be particularly true in the sleep studies. One of the ways of converting a presynaptic alpha-2 effect to an exclusively postsynaptic effect is to take away the presynaptic neuron, for example by lesioning it, so that only the postsynaptic alpha-2 effect can be expressed. In situations when the locus ceruleus is actively turned off there is no auto receptor stimulation for the alpha-2 antagonist to antagonize.

K.E. Andersson

I think it is important to point out that there are no pharmacological differences between the presynaptic and postsynaptic alpha-2-adrenoceptor that have been convincingly demonstrated. There are some drugs that are claimed to be selective for the presynaptic receptor but I do not think this is the case. I think this is a matter of selectivity and it is clear that most of those drugs, which are selective for alpha-2-adrenoceptors, at high dosages and at high concentration also will block and effect alpha-1-adrenoceptors, because the binding curves are very often biphasic. But with the dosages used in man, it is really difficult to assume that you obtain effects on

alpha-1-adrenoceptors because the drug concentrations that can be measured in plasma are really very low, and one has to consider also that the free concentration, if the drug is protein bound, is extremely low. Therefore, the drug should be assumed to act only on alpha-2-adrenoceptors.

J.T. Clark

I have three comments. One is that the animal data certainly support the paradox of excitation and inhibition because with yohimbine we see an excitation of arousal but an inhibition of erection. Another is that I do have some unpublished data that suggest that there is a shift in the dose response curve to higher doses in older rats. The third comment that I want to make relates to this last comment about postsynaptic versus presynaptic and it is that if you give some drugs that are not selective but deplete norepinephrine and/or epinephrine you attenuate the effects of yohimbine. This suggests that it would be a presynaptic effect as opposed to a postsynaptic effect.

G. Wagner

One of the technical aspects that I would like to discuss is that you arbitrarily have chosen 3 cm of increase in diameter in your evaluation of NPT. Why did you do that? Why did you not take another measure either relative to the size to that particular man's penis or to the increment of diameter? Also, you shifted at one time from 3 to 1.5 cm. in some of your evaluations and I did not quite catch why. Another point is that your volunteers were comparable age-wise to the younger group and therefore you certainly lack an older volunteers group to compare if you do the division of 45 years of age. I do not know why you did that on one occasion while on another you used 47. Finally, concerning your conclusion that a fall of noradrenergic tone might be the explanation for nocturnal erections, you should remember that if you give 3 to 5 mg of phentolamine intracavernosally you do not get a full erection, you only get tumescence. So there is never a full erection following a complete local block of the adrenergic system.

J. Bancroft

As far as the study design is concerned, you are quite right, we do not have proper control for age in relation to our dysfunctional and non-dysfunctional men. We set off first of all doing a normal volunteer study, which turned out to be in young men who wanted to do this, and we went on to do an erectile dysfunction study in men that were all thought to be psychogenically erectile dysfunctional, since they had pretty good NPTs on testing. There were an older group and we divided them simply on the basis of the median split and that happened to be 45 years in the study using visual erotic stimuli and 47 years in the sleep study. It was a very arbitrary and crude way of doing it. You are absolutely right, we cannot make a direct and conclusive comparison between our young volunteers and our younger dysfunctional men because the young dysfunctional men are a bit older. We would very much like to have an older functional group of volunteers to see whether we detect this age-related loss of responsiveness. So there are a lot of inadequacies in the design of this study design which we did not see because we were sailing in uncharted territory.

The way we presented the data, again is arbitrary. Most of the data we presented in terms of time above 15 mm increases in circumference, because generally one gets a much more modest response in the dysfunctional man. This was a variable which allowed more direct comparison. The time above 30 mm increase in circumference was more informative in the volunteers, who were getting better responses.

Your point about local adrenergic blockade is perfectly valid, and I do not think that there is yet a satisfactory explanation of why erections occur during REM sleep. I do not think it is a sufficient explanation to say there is a switch off of noradrenergic tone and yet that is, at the moment, the best I think we can do. I believe that we also have to think about serotonergic activity because there is, I understand, a switching off of serotonergic neurons during REM, and although I am not aware of any serotonergic transmission in the penis, there may well be important serotonergic transmission upstream of the penis in terms of these erectile mechanisms. The recent report of a REM-related erectile response in the rat may provide a rat model which enables some of these questions to be addressed.